The Debate over Maternal-Fetal HIV Transmission Prevention Trials in Africa, Asia, and the Caribbean: Racist Exploitation or Exploitation of Racism?

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Introduction

On September 18, 1997, an editorial appeared in the *New England Journal of Medicine*[1] denouncing the conduct of clinical trials in Africa, Asia, and the Caribbean that were designed to determine the efficacy of interventions to reduce maternal-fetal transmission of human immunodeficiency virus (HIV). The attack, signed by Marcia Angell, MD, the journal's executive editor, signaled an escalation in what had been a simmering battle over the conditions under which trials could occur involving alternatives to the standard of care in Western nations for interrupting vertical transmission of HIV. That encounter was, in turn, embedded in the far broader debate on the conditions under which research in poor Third World nations, burdened by extraordinary rates of HIV infection, should take place.

Almost 4 years earlier, in February 1994, the Data Safety and Monitoring Board of the US National Institute of Allergies and Infectious Diseases had interrupted AIDS Clinical Trial Group (ACTG) Study 076 because preliminary data revealed a statistically significant and dramatic difference in vertical HIV transmission rates in women receiving zidovudine vs those who had been given a placebo.[2] The rate for the former was 8.3%; for the latter, 25.5%. Coming at a moment of profound pessimism regarding both therapeutic prospects and vaccine development for HIV, this finding was all the more striking. The ACTG 076 regimen, which involved giving zidovudine to the pregnant woman during the last 2 trimesters, an intravenous bolus of zidovudine during delivery, and zidovudine to the newborn for 6 weeks, quickly became the standard of care.

There was, however, in all of this a bitter irony. The cost of per-patient prophylactic treatment—$800 for zidovudine alone[3]—was affordable only in industrialized nations where vertical transmission, although tragic, represented a relatively limited problem. In developing countries, however, where maternal-fetal transmission represents an epidemiologically significant disaster, the costs of prophylactic treatment (disregarding the absence of the infrastructure necessary for intravenous treatment during delivery) put treatment with zidovudine out of reach. Until recently, it was believed that 200 000 infants worldwide become infected with HIV annually. In November 1997, United Nations estimates more than doubled that figure to 580 000 newly infected infants each year. The greatest proportion of such infections occur in poor nations. In Uganda, among the poorest of Third World nations, for example, the cost of the zidovudine component of the ACTG 076 regimen represents 400 times the yearly per capita expenditure on health care.

It was, therefore, a matter of some urgency that trials begin to determine whether radically cheaper alternatives to the ACTG 076 regimen could achieve at least some measure of reduced maternal-fetal HIV transmission. In June 1994, a special consultation of the World Health Organization (WHO) considered the challenge and called for the launching of studies to achieve that goal. The consultation made clear its conclusion that placebo-controlled trials "offer the best option for obtaining rapid and scientifically valid results."[4]

In all, 16 placebo-controlled trials were launched in developing countries, including the Ivory Coast, Uganda, Tanzania, Malawi, Ethiopia, Burkina Faso, Zimbabwe, Kenya, Thailand, Dominican Republic, and South Africa. Nine of the studies were funded by the Centers for Disease Control and Prevention (CDC) or the National Institutes of Health (NIH); 5 were funded by other governments, including Denmark, France, and South Africa; and one was funded by the United Nations Program on Acquired Immune Deficiency Syndrome (UNAIDS). Fifteen of the studies involved the use of placebos.

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Critics Argue Placebo-Controlled Trials Unethical

There is no question that a placebo-controlled trial of efforts to reduce further vertical transmission in the wake of clinical trial 076 would be considered unethical in the United States or any other advanced industrial nation. No trial that denies access to the ACTG 076 regimen, or to an intervention thought to hold the promise of being at least as effective as, if not more effective than, the prevailing standard of care, would satisfy the requirements of ethical review. The question posed by the recent controversy is whether it is ethical to conduct such a trial in a poor country where the ACTG 076 regimen is out of reach as a potential therapy. (The issue is not whether the ACTG 076 would be affordable for the very limited number of research subjects. It is.) In short, can it be considered ethical to provide placebos to women in Uganda when doing so would constitute an outrage in Brooklyn? To that question, Marcia Angell responds with a thunderous no:

> Only when there is no known effective treatment is it ethical to compare a potential new treatment with a placebo. When effective treatment exists, a placebo may not be used. Instead, subjects in the control group of the study must receive the best known treatment.[1]

Given this premise, Angell rejects as irrelevant the fact that health care available in most Third World countries provides nothing like health care available in industrialized countries. Citing the Declaration of Helsinki for authority, she notes that control groups have to be provided with the best current therapy, not simply that which is available locally.

> The shift in wording between "best" and "local" may be slight, but the implications are profound. Acceptance of this ethical relativism could result in widespread exploitation of vulnerable Third World populations for research programs that could not be carried out in the sponsor country.[1]

Then, with the obvious suggestion that racism was involved, she compares the recent research studies with the infamous Tuskegee syphilis study in which poor, African-American men were studied for decades to learn the consequences of untreated venereal disease, even after effective, inexpensive therapy became available. Angell argues that the justifications used for the recent trials are reminiscent of the justifications used for the Tuskegee study.

> Women in the Third World would not receive antiretroviral treatment anyway, so the investigators are simply observing what would happen to the subjects' infants if there were no study. And a placebo-controlled study is the fastest, most efficient way to obtain unambiguous information that will be of greatest value in the Third World.[1]

Finally, Angell suggests darkly that narrow financial interests might have decided the shape of the research she attacks—clinical trials have become big business, and as in any big business, work must be done efficiently. The ethics of research, however, has a different logic, one that is not driven by considerations of efficiency above all else. To the extent that the logic of business has displaced the logic of research ethics, she warns, we have "not come very far from Tuskegee after all."[1]

Similarly Effective Interventions Proposed

However sharp the tone of Angell's editorial, it is constrained by the venue of the august *New England Journal of Medicine*. Angell was even harsher when she denounced her antagonists in an op-ed piece in the *Wall Street Journal*.

> All the rationalizations boil down to asserting that the end justifies the means—which it no more does in Africa than it did in Alabama. It is easy to see the findings of the Tuskegee study from a safe distance of 25 years. But those so offended by the comparison of the African research with Tuskegee have yet to show how these studies differ in their fundamental failure to protect the welfare of human subjects.[5]

Angell does not make clear what research would pass muster. However, given the status of the ACTG 076 regimen as the standard of care, the logic of her argument would suggest that, to be acceptable, a randomization must include the ACTG 076 regimen as the control, as well as an experimental arm that researchers have some reason to believe will be as good as, if not better than, the ACTG 076 regimen. That the limited resources of the Third World might have justified an effort to find an affordable intervention that, while effective, is less effective than the ACTG 076 regimen, would appear to Angell beyond the ethical pale.

Angell's editorial was sparked by a companion Sounding Board piece in the *New England Journal of Medicine*,[6] authored by Peter Lurie, MD, and Sid Wolfe, MD, both physicians at the Health Research Group, part of Ralph Nader's Public Citizen organization. That piece, in turn, had its origins 6 months earlier in an open letter to Secretary of the US Department of Health and Human Services Donna Shalala, denouncing the placebo studies (P Lurie et al., written communication, April 22, 1997).

In addition to being signed by Lurie and Wolfe, the open letter bears the signatures of other individuals long concerned with the ethics of research and the interests of medically vulnerable populations: George Annas, JD, Professor at the Boston University School of Public Health and a regular contributor to the *New England Journal of Medicine* on issues involving ethics; Michael Grodin, MD, Annas' colleague; and George Silver, an emeritus professor at Yale University who serves as contributing editor for the Policy Forum of the *American Journal of Public Health*.

> Unless you act now as many as 1002 newborn infants in Africa, Asia, and the Caribbean will die from unnecessary HIV infections they will contract from their HIV-infected mothers in nine unethical research experiments funded by your Department. (P. Lurie et al., written communication, April 22, 1997)

These deaths, the letter charges, could be averted if Secretary Shalala were to require that all women involved be given some regimen of zidovudine or a similarly effective intervention. Although not opposed to randomized trials, the letter's authors insist that the randomization cannot entail a denial of interventions already proven effective.

Lurie et al., like Angell, cite the Tuskegee study and see the ACTG 076 studies in Africa, Asia, and the Caribbean as racist—as involving the exploitation of people of color.

> Many people will hear in these experiments echoes of the notorious Tuskegee syphilis study. . . . This time, the people of color affected are babies from Africa, Asia, and the Caribbean, many hundreds of whom will die unnecessarily in the course of this unethical, exploitative research. (P. Lurie et al., written communication, April 22, 1997)

A Charge of Institutional Failure of Ethical Review

In underscoring the extent to which the placebo-controlled research violates international protocols governing research, the open letter by Lurie et al. cites the guidelines of the Council of the International Organization of Medical Societies (CIOMS):

> An external sponsoring agency should submit the research protocol to ethical and scientific review according to the standards of the country of the sponsoring agency, and the *ethical standards applied should be no less exacting than they would be in the case of research carried out in the sponsoring*

country [emphasis supplied in letter]. (P. Lurie et al., written communication, April 22, 1997).

Given the thrust of the CIOMS principles as well as those of the WHO enunciated in the Declaration of Helsinki and the Nuremberg Code, it is remarkable, the letter's authors note, that the placebo-controlled studies passed ethical review. Although the proponents of placebo-controlled trials would point to such oversight to justify the challenged research, Lurie et al. see in the approval of the trials a sign of institutional failure, even corruption: Researchers in developing countries are from higher social classes than those who are research subjects, and, thus, those researchers are unlikely to safeguard their subjects' interests. The lure of collaboration might simply overcome ethical scruples, given the "obvious benefits in prestige and, perhaps, in salary" (P. Lurie et al., written communication, April 22, 1997).

Affordability of Similarly Effective Interventions

A second and very different charge in the letter to Secretary Shalala underscores the claim that the placebo-controlled trials are exploitative of poor people, who are being manipulated into serving the interests of those who live in wealthy nations. Although the new strategies being examined might be less costly than the ACTG 076 regimen, they may still be unaffordable in the nations being used for testing. In that case, the new knowledge only provides cheaper options for industrialized nations (P. Lurie et al., written communication, April 22, 1997).

Surprisingly, having made this charge, the authors of the letter to Secretary Shalala go on to make clear that the only research that would be acceptable would raise the very questions of affordability.

> We are, therefore, not opposed to research that modifies the regimen provided in Protocol 076 in order to identify a simpler, less expensive, similarly effective or more cost-effective intervention. . . . For example, one study arm could receive AZT [zidovudine] and the other AZT [zidovudine] and the experimental prophylactic regimen. (P. Lurie et al., written communication, April 22, 1997)

Equivalency Trials Accepted by Some—New Interventions Proposed

When this letter at last made its way into the *New England Journal of Medicine* as a Sounding Board piece[6] published together with Marcia Angell's editorial, it took a significantly different form from the open letter sent to Secretary Shalala—the 1002 babies who would die because of unethical research now became, more vaguely, "hundreds of babies." Rather than focusing on the claim that it was by definition unethical to conduct a placebo-controlled trial in the post–clinical trial ACTG 076 era, Lurie and Wolfe now asserted that, given the evidence of ACTG 076 itself, it is appropriate to conduct equivalency trials. Thus, their moral outrage is muted in the service of a set of methodological claims.

An equivalency trial, they point out,[6] is conducted when a regimen has already been proven effective and when there is interest in determining whether a second regimen is about as effective but less toxic or expensive. Given the results of the ACTG 076 clinical trial, it was clear, Lurie and Wolfe aver, that shorter regimens would be more effective than placebos. They write: "These findings seriously disturb the equipoise (uncertainty over the likely study result) necessary to justify a placebo-controlled trial on ethical grounds. . . ."[6] More critically, they claim that there is good reason to be optimistic that "researchers are quite capable of designing a shorter antiretroviral regimen that is approximately as effective as the ACTG 076 regimen."[6]

This reading of the data available when the placebo-controlled trials were being launched has not gone unchallenged. Jeffrey Laurence, director of the Laboratory for AIDS Virus Research at the New York Hospital–Cornell University Medical College, notes, for example, that the less costly interventions are "certain to be less effective than the standard regimen."[7]

By way of summary, then, those who have opposed the recent trials have done so for a number of not always compatible reasons. Some have argued that, in the aftermath of clinical trial ACTG 076, research subjects in randomized trials must have access to the prevalent standard of care in the West; that zidovudine should be affordable for the limited numbers enrolled in trials; and that a zidovudine-based control arm should be provided to research subjects regardless of local prevailing medical practice. Some have been simply offended by the use of placebos in the trials conducted after ACTG 076, and they have urged comparisons of new interventions against historical controls, i.e., local experience with untreated populations. Finally, some, like Lurie and Wolfe, have asserted that, because the time is ripe for equivalency trials, placebos are methodologically unwarranted.

Placebo-Controlled Trials Defended; Changes Proposed

A formal public response to the challenge in the *New England Journal of Medicine* appeared 2 weeks later on October 2, 1997,[3] signed by David Satcher, director of the CDC, and Harold Varmus, director of the NIH (the timing was possible only because information about the planned publication of the Lurie-Wolf editorial had been leaked). Locating the criticized trials in the context of the profound poverty of many nations where vertical transmission is so critical an issue, Satcher and Varmus make clear in their letter that placebo-controlled trials were dictated by the urgency of the situation.

Nevertheless, they reject as "too simple" the argument that, because most women in the countries where placebo-controlled trials have been conducted received no care before participating in the trials, placebos represented no additional risk above standard practice. Satcher and Varmus thus seek to distance themselves from the charge that the research under attack took advantage of the poverty of the women involved. They also reject the argument that such trials could produce faster results with fewer subjects. More aggressive recruitment, they note, might have expedited the trial results.

Satcher's and Varmus' willingness to forgo these justifications reflects their extraordinary effort to neutralize the charge that narrow, economic concerns provided the warrant for research designs that involved a misuse of poor subjects. Thus, Satcher and Varmus lose the opportunity to engage the question of whether prevailing conditions in many Third World countries could justify trials that would not require "very large numbers of women in order to see a statistically significant improvement."[7] They also lose the opportunity to examine the difficult ethical question of how one should balance the claims of research subjects and their offspring against the claims of those who might be placed at risk if the use of nonplacebo designs were to require trials of more extended duration. Time is not an ethically neutral consideration, given that, in the period before definitive answers become available, untreated mothers and their offspring continue to suffer the risk of vertical transmission.

In the end, Satcher and Varmus, like Lurie and Wolfe, seek a methodological rationale for their claims. Only placebo-controlled trials, they argue, can provide "definitive," "clear," "firm" answers about which interventions have worked, thus allow-

ing governments to make "sound judgments about the appropriateness and financial feasibility of providing the intervention."[3]

On methodological grounds, Satcher and Varmus argue that testing 2 or more interventions of unknown benefit against each other would not make clear whether either intervention would prove more effective than no intervention. In addition, even if one intervention were superior, it might be difficult to determine the extent of the advantage because the interventions might differ in other ways, e.g., in terms of toxicity or cost. Further, they point out, comparing an intervention of unknown benefit against the ACTG 076 regimen, which is likely to be more effective, would be of little use if the ACTG 076 regimen were unaffordable and therefore unavailable. Finally, the failure to employ a placebo control would make it difficult to clearly determine whether the affordable but less effective intervention is better than no intervention at all. In short, they conclude, placebos are crucial to policymakers required to make relatively costly decisions under conditions marked by profound poverty and scarce public health resources.

To bolster their argument, Satcher and Varmus underscore the extent to which consultation with host country scientists, physicians, and others has produced agreement on research design. Indeed, they quote Ugandan physician Edward Mbidde, MD, chair of the AIDS Research Committee: "These are Ugandan studies, conducted by Ugandan investigators, on Ugandans, for the good of their people."[3]

However heartfelt Mbidde's observation may be, it would be easy to challenge as involving an overstatement of the provenance of the research on vertical transmission. Likewise, one can easily imagine how Lurie and Wolfe would characterize such support, since they so contemptuously decry the self-interest of craven host-nation researchers.[6] Nevertheless, local groups' consent to and collaboration in the research under challenge creates a far more complex picture than is suggested by the image of Western scientific imperialism imposing its will on hapless neocolonial societies.

Conclusion

The invective that characterizes the controversy outlined above is striking, in part because, despite assertions to the contrary, this debate is not an instance of the ongoing clash between those—called ethical imperialists by some, universalists by others—who believe that a single Western-dominated ethical standard should apply to all research and others who believe that ethical standards for research should reflect local values. Rather than a clash over first principles, this is a dispute over the application of agreed-upon principles in radically different social conditions. The controversy is also striking because persons with well-known commitments to the protection of the rights of research subjects find themselves confronting each other across a bitter divide.

Among those who have publicly supported the use of placebo-controlled trials are Arthur Amman, MD, president of the American Foundation for AIDS Research; Robert Levine, MD, of Yale University, long-time editor of *IRB: A Review of Human Subjects Research* and author of the standard text *Ethics of Regulation of Clinical Research*[8]; and Norman Fost, MD, a pediatrician and director of the Medical Ethics program at the University of Wisconsin, Madison. Among the trials' opponents, in addition to Marcia Angell, are Jonathan Mann, MD, former director of the WHO Global Programme on AIDS and a well-known advocate for human rights in the context of public health practice; Arthur Caplan, PhD, director of the Medical Ethics Program at the University of Pennsylvania and perhaps the most widely cited bioethicist in America; George Annas; and, of course, Lurie and Wolfe. Many remain conflicted or agnostic, most notably Ruth Faden, PhD, director of the Bioethics Institute at the Johns Hopkins University and former chair of the presidential commission established to examine the abuse of subjects in the context of radiation experiments.

This deep divide among the deeply committed at once explains the debate's fury and provides a clear sign that the issues involved are complex and not easily reduced to posturing and sloganeering. It is, therefore, especially troubling that the scandal of Tuskegee has been invoked to denounce the recent trials. Tuskegee was both cruel and deceptive: there was not even the pretense of informed consent, and ultimately the poor African-American men involved in that study were willfully deprived of socially affordable therapy for the treatment of their syphilis. Indeed, every effort was made, through dissimulation, to keep those men from gaining access to effective therapy. In the trials under attack, however, women have given their informed consent, however problematic,[9] and the studies have been examined by local review committees and an ethics committee of UNAIDS. Perhaps most important, everyone acknowledges that the ACTG 076 regimen is not socially affordable in most nations, given the price of zidovudine and the infrastructure requirements for its administration.

The tragedy of the recent trials is that they bear a profound moral taint, not of a malevolent research design but, rather, of a world economic order that makes effective prophylaxis for the interruption of maternal-fetal HIV transmission available but unaffordable for many—this is true, as well, for a host of treatments for AIDS and other diseases. In a just world, this would not be the case and the very research under attack would be unnecessary. It is the social context of maldistribution of wealth and resources that both mandates these studies and, at the same time, renders them so troubling. □

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